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MS APPEAL BRIEF - PATENTS
PATENT
0230-0161P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of		Before the Board of Appeals	
Kenji ASANO et al.		Appeal No.:	
Appl. No.:	09/856,718	Group:	1654
Filed:	January 28, 2002	Examiner:	COE, S.D.
Conf.:	3333		

For: LAK ACTIVITY ENHANCERS DERIVED FROM EXTRACT OF LENTINUS EDODES MYCELIUM AND LAK ACTIVITY-ENHANCING FORMULATIONS CONTAINING THE EXTRACT

APPEAL BRIEF TRANSMITTAL FORM

MS APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 20, 2004

Sir:

Transmitted herewith is an Appeal Brief (in triplicate) on behalf of the Appellants in connection with the above-identified application.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. § 1.8.

A Notice of Appeal was filed on June 17, 2003.

☐ Applicant claims small entity status in accordance with 37 C.F.R. § 1.27

The fee has been calculated as shown below:

☒ Extension of time fee pursuant to 37 C.F.R. §§ 1.17 and 1.136(a) - $1,590.00.

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☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this sheet is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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0230-0161P

Attachment(s)

(Rev. 11/04/03)

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A P P E A L B R I E F

January 20, 2004
(Tuesday after holiday)

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BRIEF ON BEHALF OF APPELLANT

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APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 20, 2004
(Tuesday after holiday)

Sir:

In response to the Examiner's Office Actions dated December 17, 2002, and the Advisory Actions dated October 1, 2003 and December 11, 2003, the following Appeal Brief is respectfully submitted in connection with the above-identified application.

I. Real Party in Interest

The present application is a National Stage application of International Application PCT JP99/06616. The "Applicant" of the International Appplication is Kobayashi Pharmaceutical Company, Ltd. of Osaka, Japan. No Assignment of the present application from the inventors Kenji Asano, Yukiko Matsuda and Yutaka Tajima to Kobayashi Pharmaceutical Company, Ltd. has yet been recorded in the USPTO.

II. Related Appeals and Interferences

No appeal or interference involving a related application is known to Applicants' Representative.

III. Status of the Claims

Claims 1-10 and 12-20 are pending. Claim 11 has been canceled.

Claims 1-10 and 12-20 stand rejected under 35 U.S.C. § 103(a) over U.S. Patent 4,461,760. The decision of the Examiner in the Advisory Action of October 1, 2003 to maintain this rejection is appealed.

The text of the appealed claims is provided as Appendix I attached hereto.

IV. Status of Amendments

A Reply Under 37 CFR 1.116 was filed on April 17, 2003. The Advisory Action of October 1, 2003, indicates that the Amendment was entered.

A second Reply under 37 CFR 1.116 was filed on October 17, 2003. That paper suggested no amendments to the claims, but its arguments were considered by the Examiner but deemed not to overcome the remaining rejection as indicated in the Advisory Action of December 11, 2003.

V. Summary of the Invention

Treatment of peripheral lymphocytes with certain compounds, for example interleukin-2, produces an activated, heterogeneous population of cells called, "lymphokine activated killer cells" or "LAK" cells (paragraph bridging pp. 2-3). One embodiment of the present invention is a composition having the biological activity of producing LAK cells when used to treat peripheral lymphocytes, or of increasing the anti-tumor activity of LAK cells (p. 7, lines 1-4). The composition comprises an extract of *Lentinus edodes* mycelia (p. 7, lines 19-20). In general, the extract is prepared by crushing and delignifying a culture of *Lentinus edodes* mycelia in the presence of water and added enzymes (p. 10, lines 19-24). The extract can be formulated for pharamaceutical or veterinary use and for different routes of

administration, including injection or oral administration, or as a food additive (p. 8, lines 6-16).

For activation of peripheral lymphocytes, the composition of the invention is typically added to the lymphocytes such that 1 µg to 1 mg of the extract is provided to 10^6 lymphocytes (p. 12, line 22).

Another embodiment of the invention is use of the composition to enhance LAK activity of lymphocytes by either contacting peripheral lymphocytes or LAK cells with the composition in culture (p. 12, lines 5-29) or by injection into a subject (p. 13, line 1-5). LAK cells treated with the composition may be reinfused into a subject for immunotherapy (p. 12, line 10). Treatment can be for generalized improvement of immune function or for treatment of cancers (p. 8, lines 17-28). Treatment of tumors is not direct, but is mediated by the induction of LAK cell activity in the patient (p. 8, lines 20-21).

VI. Issues for review by the Board

Appellants submit that the rejection of claims 1-10 and 12-20 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 4,461,760 ("the '760 patent") raises the following issues for consideration by the Board of Appeals:

1. Does the Examiner correctly establish *prima facie* obviousness of claim 20, directed to a process comprising crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

2. If the Examiner has properly established *prima facie* obviousness of the invention of claim 20, is there evidence of record sufficient to rebut *prima facie* obviousness?

3. Once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes, is an obviousness rejection of the claims over the same reference legally tenable?

4. Does the Examiner correctly establish *prima facie* obviousness of claims 1-9, directed to a composition that is prepared by a process of crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

5. If the Examiner has properly established *prima facie* obviousness of the invention of claims 1-9, is there evidence of record sufficient to rebut *prima facie* obviousness?

6. Is claim 10, directed to a method for treating cancer or tumors by administering a formulation of claim 1, allowable if claim 1 is unobvious?

7. Does the Examiner properly establish *prima facie* obviousness of claims 12-18, directed to methods for enhancement of LAK activity in lymphocytes, over the disclosure of the '760 patent?

8. Does the Examiner properly establish *prima facie* obviousness of claims 3 and 14, which recite a range of 1 μg or more of an extract of *Lentinus edodes* per 10^6 lymphocytes, over the disclosure of the '760 patent?

9. Does the Examiner properly establish *prima facie* obviousness of claim 19, directed to a method for treating cancer by enhancing LAK activity by administering a composition that is prepared by a process of crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

VII. Grouping of the claims

Appellants submit that the following groups of claims raise separate issues for consideration by the Board of Appeals.

Group I, claim 20, raises issues 1 and 2 for consideration.

Group II, claims 1-9, raises issues 3, 4 and 5 for consideration.

Group III, claim 10, raises issue 6 for consideration.

Group IV, claims 12-18, raises issue 7 for consideration.

Group V, claims 3 and 14, raises issue 8 in addition to issues 3-5 for consideration.

Group VI, claim 19, raises issue 9 for consideration.

VIII. Argument

Group I

Claim 20 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the '760 patent. This rejection raises for consideration by the Board the questions of whether the Examiner has properly established *prima facie* obviousness of the invention (Issue 1). If the Board determines that the Examiner has properly established *prima facie* obviousness of the invention, the Board must then go on to consider whether there is any evidence of record that establishes unobviousness of the invention (Issue 2).

The Examiner fails to establish proper prima facie obviousness of the process described by claim 20

The Examiner bears the initial burden of establishing *prima facie* obviousness of the claimed invention. The claim is granted to the Applicant (Appellant) if the Examiner fails to meet this initial burden. *In re Oetiker,* 24 USPQ2d 1443 (Fed. Cir. 1992). For the Examiner to establish a proper case of *prima facie* obviousness, the references cited must describe or suggest any specific modification of the reference, no matter

how minor, to obtain the invention from the disclosure of the reference. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1324 (Fed. Cir. 1991). There must also be motivation, provided by the reference itself or by the state of the art at the time the invention was made, to so modify the teachings of the reference to obtain the invention. *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999). Motivation to modify the teachings of the reference must be found even if, as in the present case, only a single reference is cited in making the rejection. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 37 USPQ2d 1314, 1318 (Fed. Cir. 1996). Appellants submit that both of these elements of *prima facie* obviousness are absent from the standing rejection.

The claimed invention

Claim 20 recites:

> A method of preparing a LAK activity enhancer which comprises
>
> preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of ***additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase***, wherein said solid medium is based on bagasse and defatted rice bran; and
>
> raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s). (Emphasis added.)

The teachings of the '760 patent

The portion of the '760 patent that describes extraction of mycelia of *Lentinus edodes* is found at col. 2, line 61 to col. 3, line 20 and reads as follows:

> The crushed medium (the mixture of mycelium and the medium, which is called the nutrient medium and tissue-medium hereinafter) was packed in a tank, and after adding 5 liters of water at pH 3 to 8 per 800 grams of the nutrient medium and tissue-medium, it was blended and stirred stepwise for a given period of time: that is the temperature was changed in the range from 40° C. to 60° C. depending on pH for promoting enzymation ***according to activities of enzymes such as cellulase, chitinase, glucosidase and protease existing in the nutrient medium and tissue-medium***. Finally it was blended and stirred at 80° C. for deactivating the enzymes, and in this step the mycelial components, the metabolites of mycelia, and cellulose decomposition products of the medium component were dissolved in water.
>
> The suspension thus obtained was packed in a filtering bag of flannel, and compressed to filter, and the filtrate was further filtered through a membrane filter and sterilized to obtain an extracted solution.
>
> The extracted solution thus obtained was freeze-dried and a powder (which is called as LEM hereinafter) was obtained. To the aqueous solution of LEM, ethyl alcohol of 4-fold volume of the LEM solution was added, and the precipitate produced was washed with 80% ethyl alcohol twice, and then centrifuged and freeze-dried to obtain a powder (which is called as LAP hereinafter). (Emphasis added.)

The '760 patent discloses that the extract so produced has antitumor activity (*e.g.* col. 2, line 43). Important to the instant question, the '760 patent discloses (at col. 8, lines 27-32) that the antitumor activity is found in a fraction that is,

> ...mainly composed of xylose, as described above, and also had considerable amounts of glucose, galactose,

> mannose and arabinose. These results clearly reflected the polysaccharide composition of the medium, and the fact that xylose is the main sugar in place of glucose strongly suggests the relation with the activity of the enzyme of mycelia of C. shiitake.

The differences between the invention and the teachings of the reference

During prosecution to date, Appellants have argued that the present claim 20 includes addition of one or more cellulase, protease or glucosidase enzymes to the crushed mycelia and medium composition to digest the mixture. On the other hand, the '760 patent teaches that the mycelia and the medium are to be decomposed solely (after the crushing) by the action of enzymes as are originally present in the cells or the medium. (Note the text highlighted above.)

The Examiner takes a position that the addition of the enzymes is obvious. She argues that the substitution of exogenous enzymes for the endogenous enzymes would be routine, as the enzymes are merely added for their known purpose of digesting the culture medium and cells and that the knowledge of the skilled artisan that such is the activity of these enzymes provides the requisite motivation.

Appellants disagree. First, the claimed invention is not a mere substitution of exogenous enzymes for endogenous ones. Rather, as described in claim 20, it is addition of exogenous enzymes. Nothing is done to inactivate or remove the endogenous

enzymes. The '760 patent clearly states that enzymes "existing in the nutrient medium and tissue-medium" are sufficient to digest the culture. There is no suggestion whatsoever that any advantage is obtained by altering the enzyme content of the culture during the digestion process. Indeed, the '760 patent expressly describes that the antitumor activity of the extract is related to the enzyme composition of the mycelia of the mushroom. Therefore, the '760 patent in fact strongly suggests that the enzyme content of the digestion should not be altered.

Appellants note that there is no characterization in the '760 patent of the particulars of the enzymes produced during the culturing, other than to say that the pH of the digestion must be optimized, and therefore the relative amounts of chitinase, cellulase, protease and glucosidase activities are unknown. Also unknown is the nature of the antitumor component that is obtained from the extract. Appellants submit that the scientific method is characterized by controlling variables, so as to minimize changes between experiments. Thus, the skilled biochemist, rather than being motivated to alter the uncharacterized mixture of the digesting culture by increasing the activity of any enzyme during the digestion, would be motivated to leave it be, so as to avoid inadvertantly inactivating the (also uncharacterized) antitumor component obtained in the extract. Such conservatism is indeed justified

in view of the express teaching of the '760 patent that the endogenous enzyme composition is important to obtaining an antitumor activity in the resulting extract. It seems the Examiner has substituted her own thinking for that of the artisan of ordinary skill to allege motivation.

Thus one can see that the '760 patent fails to describe or suggest at least one modifications of its teachings that are features of the instant claim 20, the addition of enzymes to the culture during digestion. In fact, the '760 patent expressly urges against this. One can also see that the Examiner's allegation of motivation fails in that her speculation regarding motivation is contrary to an express teaching of the '760 patent.

Accordingly, two elements of a proper *prima facie* case of obviousness are absent from the rejection of claim 20 under 35 U.S.C. § 103(a) over the '760 patent. Therefore this rejection must be reversed.

There is evidence of record of differences between the extract resulting from the process of claim 20 and the extracts disclosed by the '760 patent and this is unexpected and sufficient to rebut prima facie obviousness

If the Board should agree that the Examiner has properly established *prima facie* obviousness of claim 20, the Board must then consider whether there is evidence of record sufficient to rebut that conclusion. Appellants submit that there is evidence

in the record that the process of claim 20 provides a composition that is distinct from the composition of the extracts characterized in the '760 patent. Appellants submit that this is an unexpected result and sufficient evidence to rebut *prima facie* obviousness.

An exemplary extract obtained by the process of claim 20 is described in Example 1 of the specification and is characterized as to chemical content at p. 21, line 25 to p. 22, line 7. There the extract is described as being composed of 25.3% carbohydrate, 19.7% protein, 2.6% polyphenols, 8% crude fat, 22% crude ash and about 20% soluble nitrogen-free materials other than carbohydrate. These last four amounts might be summed as 52.6% "other".

Furthermore, the carbohydrate component is further analyzed as being 15.2% xylose, 8.2% arabinose, 8.4% mannose, 39.4% gulose[1], 5.4% galactose, 12.0% N-acetylglucosamine and 11.3% glucuronic acid.

The comparable extract in the '760 patent is designated "LEM", or "LAP" after alcohol precipitation and lyophilization. LAP is characterized in Table 1 at col. 3 as being composed of 24.8% (248 µg/mg) protein, 57.6% sugar and 17.6% (other). While the carbohydrate contents are not analyzed for the same sugars

[1] The specification indicates "Gul". It is not entirely clear to Appellants' Representative if this is to represent "gulose" or is a typographical error and Glu, for "glucose" is intended. If the latter, the Board might note that the LAP extract contains 19.9% glucose.

entirely, the xylose content is 30.2%, the galactose content is 20.3%, the arabinose content is 17.4% and the mannose content is 9.5%. At least these sugars are greatly different in their amounts and proportions compared to the extract obtained by the process of claim 20.

Furthermore, the Examiner has asserted during prosecution that the composition of claims 1, 2 and 4-10 was inherently the same as the product of the process described in the '760 patent. In the response of September 30, 2002, Appellants pointed out that the product of the process as described in claim 1, which recites the same steps as the process of claim 20, comprises approximately 40% glucose[2]. On the other hand, the LAP-1 and LAP-2 compositions of the '760 patent, which are chromatographic fractions of LAP, comprise 39.0% and 30.4% xylose, respectively. The Examiner accepted this evidence of distinction between the composition of the present invention and that produced by the process of the '760 patent and withdrew the rejection under 35 U.S.C. § 102.

Appellants submit that presentation of an anticipation rejection based upon inherency constitutes an admission by the Examiner that the expectation of the one of skilled in the art is that the modification of the process of the '760 patent by the addition of one or more of cellulase, protease and

[2] This may be in error, in that, as noted above, the specification indicates "Gul".

glucosidase would result in the same product. Therefore, finding differences between the extract made by the process of claim 20 and that obtained by the process of the prior art must therefore be a result obtained by the process of claim 20 that is unexpected by the artisan of ordinary skill.

Appellants submit that, even if the Board should hold that the Examiner has established *prima facie* obviousness of the process of claim 20 in view of the '760 patent, the differences overall composition, and especially in distribution of carbohydrate among different sugars between the extract prepared in Example 1 of the instant application and the LAP extract described in the '760 patent, are sufficient evidence of unobviousness to rebut the Examiner's assertion. Accordingly, the rejection of claim 20 under 35 U.S.C. § 103(a) as unpatentable over the '760 patent may also be reversed on this basis and Appellants respectfully request such favorable action.

Group II

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This rejection raises for consideration by the Board the issue of whether once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes, a

rejection of the claims over the same reference is legally tenable (Issue 3). If so, then this rejection also raises the issue of whether the Examiner has properly established *prima facie* obviousness of the claimed extract (Issue 4). If the Board determines that *prima facie* obviousness is indeed established, then they must consider whether there is evidence of record sufficient to establish unobviousness of the invention (Issue 5).

Once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes an obviousness rejection of the claims over the same reference is not legally tenable

The present claim 1 recites:

> 1. A LAK activity enhancer containing an extract of Lentinus edodes mycelium, which is prepared by preparing a suspension by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more ***additive enzymes selected from the group consisting of cellulase, protease and glucosidase,*** wherein the solid medium is based on bagasse and defatted rice bran; and raising the temperature of the suspension to about 80-100°C to inactivate the enzymes. (Emphasis added.)

Claims 2-9 are dependent ultimately from claim 1.

Thus, claims 1-9 are "product-by-process" claims.

Typically, patentability of product-by-process claims is evaluated without reference to the specific process steps. When an Examiner provides a reference that discloses a product of a closely similar process, the Examiner can properly take a

position that a product of that process is expected to be the same as the claimed product in support of a rejection for anticipation based upon inherency. The burden of persuasion then shifts to the Applicant (Appellant) to show by a preponderance of the evidence that the claimed product is different. *In re Fitzgerald,* 205 USPQ 594 (CCPA 1980).

Such has been the course of prosecution of claims 1, 2 and 4-10 to this point, but the Examiner now makes an obviousness rejection (of claims 1-10) over the same single reference used to assert anticipation. This cannot be a proper rejection.

Prima facie obviousness is a legal theory that shifts the burden of proof. The Examiner bears an initial burden of establishing obviousness of the invention by the preponderance of the evidence. When the Examiner establishes *prima facie* obviousness, the burden of persuasion shifts to the Applicant (Appellant) to rebut the conclusion of obviousness by evidence establishing unobviousness of the invention. *In re Piasecki,* 223 USPQ 785 (Fed. Cir. 1984). Evidence of a result of the invention not expected by the artisan of ordinary skill is typically sufficient. *In re Soni,* 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), *In re Mayne,* 42 USPQ2d 1451, 1454 (Fed. Cir. 1997).

Making a rejection for anticipation based upon inherency represents a conclusion by the Examiner that identity of the products of the process described by the reference and of the

process described in the claim is the expectation of the skilled artisan. Overcoming of the rejection based upon inherency by evidence of differences between the products establishes the sufficiency of the evidence to show a result not expected by one of ordinary skill in the art. By withdrawing the rejection, the Examiner admits the evidence has been found sufficient to rebut a presumption of anticipation, the epitome of obviousness (*Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984)), and therefore must also be sufficient to rebut any rejection for obviousness over the same reference.

In such an instance making or maintaining a rejection under 35 U.S.C. § 103(a) based upon the same reference is therefore not legally supportable.

As explained above, Appellants have overcome a rejection of claims 1, 2 and 4-11 for anticipation over the '760 patent based upon inherency. (See paragraph 5 of the Office Action of December 17, 2002, Appellants' reply of April 17, 2003 and the Advisory Action of October 1, 2003, advising that the rejection under 35 U.S.C. § 102 had been overcome by Appellants' response.) The rejection was overcome by explaining and providing evidence from the respective specifications of differences between the product-by-process of claim 1 and the product obtained by the process of the '760 patent.[3] These

[3] Thus, the facts of the present application distinguish it from the case of *Fitzgerald, supra*.

differences in composition are explained in detail above and the Examiner found them to be sufficient evidence to rebut her presumption of identity. Appellants submit that the evidence of differences must therefore also be sufficient to establish unobviousness of the product claimed in claim 1 over the product of the '760 reference. The standing rejection of claims 1-9 as being obvious over the '760 reference should therefore fail by operation of law.

The Examiner fails to establish proper prima facie obviousness of the extract described by claims 1-9

The '760 patent does not disclose or suggest each and every specific modification of its teachings to obtain the invention of claims 1-9. Neither is there any motivation to modify what is taught by the '760 patent to arrive at the invention described by claims 1-9.

As explained in detail with respect to claim 20, the '760 patent fails to disclose or suggest that an extract of *Lentinus edodes* mycelia should be made by a process that includes a step of digesting a culture of the mycelia with added enzymes selected from at least one of cellulases, proteases and glucosidases. There is no disclosure or suggestion that any enzymes not already present in the culture should be added.

Also, the Examiner fails to provide any sufficient allegation of motivation to modify the teachings of the '760

patent to achieve the invention of claims 1-9. The Examiner has not provided any evidence or sound reasoning of motivation, but has merely speculated, incorrectly, that a skilled biochemist would make the modification suggested by the Examiner. Therefore, the Examiner has failed to properly establish *prima facie* obviousness of the claimed invention. Accordingly, the standing rejection of claims 1-9 under 35 U.S.C. § 103(a) over the '760 patent should be reversed.

There is evidence of record that composition of the extract is unexpectedly different from the extract of the '760 patent

Furthermore, as explained above, there is evidence of record that the process steps recited in claim 1 and the process described in the '760 patent result in differenT compositions of the extract that is obtained.

Again, an exemplary extract obtained by the process of claim is described in Example 1 of the specification and is characterized as to chemical content at p. 21, line 25 to p. 22, line 7. The extract product according to the instant claim 1 is shown by comparison of these descriptions to have a different proportion of protein, carbohydrate and "other substances" from the LAP composition of the '760 patent. Furthermore, to the degree the carbohydrates of each extract are characterized, the proportion of different sugars in the claimed extract is

substantially different from the LAP, LAP-1 and LAP-2 preparations of the '760 patent.

The Examiner has admitted by her presentation of an inherency rejection that one of ordinary skill in the art would expect the composition of claim 1 to be identical to the composition of the '760 patent. Therefore, differences in the compositions must be taken as a result that would be unexpected by one of skill in the art who reads the '760 patent.

Therefore, there is evidence of record sufficient to establish an unobvious distinction between the product of the instant claim 1 and the product described in the '760 patent. Accordingly, the rejection of claims 1-9 under 35 U.S.C. § 103(a) over the '760 patent may be reversed on this basis as well. Appellants respectfully request such favorable action.

Group III

Claim 10 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This rejection raises the issue of whether claim 10, directed to a method for treating cancer or tumors, must be considered unobvious over the '760 patent if claim 1 is considered unobvious over the '760 patent (Issue 6).

Unobviousness of claim 1 establishes unobviousness of claim 10

Appellants submit that, should the Board find claim 1 unobvious, then claim 10 must also be deemed unobvious.

Claim 10 recites:

> 10. A method for treating tumor and/or cancer comprising administering an effective amount of the LAK activity-enhancing formulation of claim 4.

Claim 4 is dependent upon claim 1, and therefore claim 10 is a method of use of the "product-by-process" described by claim 1.

For all of the reasons described above, Appellants have established that the product that is administered in the method of claim 10 is not obvious over the '760 patent and claim 1 is therefore allowable over the reference. Claim 10 is commensurate in scope with the product claim asserted by Appellants to be allowable. Accordingly, claim 10 should also be found patentable over the '760 patent. M.P.E.P. 821.04.

Group IV

Claims 12-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 reference. This rejection raises the issue of whether the Examiner has properly established *prima facie* obviousness of the invention described in claims 12-18 (Issue 7).

The Examiner does not properly establish prima facie obviousness of the methods of claims 12-18 over the disclosure of the '760 patent

Appellants submit that the Examiner has failed to establish proper *prima facie* obviousness of the invention of claims 12-18 over the disclosure of the '760 patent. In particular, the reference fails to disclose or suggest one or more specific modifications of its teachings to make the claimed invention. Furthermore, there is no motivation put forth on the record to modify the teachings of the '760 patent to obtain the invention that is described by claims 12-18.

The claimed invention

Claim 12 recites:

> 12. A method for ***enhancing LAK activity*** which comprises administering to a mammal ***a therapeutically effective amount of LAK activity enhancer*** containing an extract of Lentinus edodes mycelium, which is prepared by:
>
> preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and ***one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase***, wherein said solid medium is based on bagasse and defatted rice bran; and
>
> raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).

Claims 13-18 depend from claim 12.

The teachings of the '760 patent

The '760 patent describes an extract of *Lentinus edodes* that is applied directly to tumor cells for its tumor cell-killing activity. For example, at col. 2, line 43, the '760 patent describes that the extract, "acts only upon cancerous cells". Furthermore, in the working Examples experiments measuring the proliferation of ascities tumor cells *in vivo* are performed. See, (G) at col. 6. There is no description at all of any experiments using lymphocytes or any blood or immune cell.

Differences between the invention and the '760 patent

As emphasized in the text of claim 12 above, the instant invention is a method for enhancing LAK cell activity. The method has as one of its results an effect of tumor killing. However, the claimed method is more general; it can be applied for general enhancement of immune function. *See*, p. 8, lines 17-24. The instant specification makes quite clear that the extract of the present invention does not specifically attack tumor cells. *See*, p. 8, lines 20-21. This is reflected in claim 12, which recites a method for enhancing LAK activity.

Furthermore, the instant claim 12 recites that the extract to be applied is one prepared by a process that includes adding one or more enzymes that is a cellulase, a protease or a

glucosidase to a digestion of a culture of *Lentinus edodes* mycelia. As has been explained in detail above, this process for producing the extract is not described in the '760 patent. Neither is there any suggestion made to modify the process that is described in the '760 patent to make such an extract.

Finally, the instant claim 12 recites that a "therapeutically effective amount of LAK activity enhancer" is administered. The '760 patent makes no disclosure or suggestion of what might be a therapeutically effective amount of a LAK activity enhancer might be. Of course, the '760 patent cannot include such disclosure or suggestion, as the '760 patent is all about an extract that acts upon tumor cells, not upon lymphocytes.

As there is no disclosure or suggestion in the '760 patent of any of the above differences between the invention and the teachings of the reference, it is plain that the specific modifications of the disclosure of the '760 patent to make the claimed invention are not taught or suggested by the reference.

Furthermore, the Examiner has never set forth on the record any kind of motivation to produce an extract for purposes of enhancing LAK activity. The Examiner has not mentioned any reason, put forward by a reference or by any reasoned statement of the Examiner, to develop any method for enhancing LAK

activity of lymphocytes, and especially for developing any such method using an extract of *Lentinus edodes*.

As the '760 patent fails to disclose or suggest specific modifications of its disclosure to obtain every feature of the instant claims 12-18, and the record does not contain any motivation to modify the teachings of the '760 patent to make the present invention, the Examiner fails to establish a proper *prima facie* case of obviousness of claims 12-18 over the '760 patent. Accordingly, the rejection of claims 12-18 under 35 U.S.C. § 103(a) over the '760 patent should be reversed and such favorable action is respectfully requested.

Group V

Claims 3 and 14, dependent upon claims 1 and 12, respectively, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. Claims 3 and 14 recite as a feature in addition to those of claims 1 and 12 that the amount of the extract in the composition (claim 3) or applied in the method (claim 14) is "at a concentration of 1 μg or more per 10^6 lymphocytes".

Appellants submit that the instant rejection raises for consideration by the Board the issue of whether the Examiner properly establishes *prima facie* obviousness of claims 3 and 14, which recite a range of 1 μg or more of an extract of *Lentinus*

edodes per 10^6 lymphocytes, over the disclosure of the '760 patent (Issue 8). Appellants submit that she has not.

The Examiner does not properly establish prima facie obviousness of claims 3 and 14 over the disclosure of the '760 patent, in view of their recitation of the range of 1 μg or more of an extract of Lentinus edodes per 10^6 lymphocytes

The invention described in the instant claim 14 is a method for enhancing LAK activity of lymphocytes. Claim 12, from which claim 14 depends, describes administering a "therapeutically effective" amount of an extract of *Lentinus edodes* to achieve this. Claims 3 and 14 recite a particular dosage range that is described as a mass of the extract per number of lymphocytes. That is, a "therapeutically effective amount" is described in claims 3 and 14 as "at a concentration of 1 μg or more per 10^6 lymphocytes".

On the other hand, the '760 patent describes use of an extract of *Lentinus edodes*, which is established above to be substantially different from the extract applied in the present invention, to directly kill tumor cells. There is no description or suggestion in the '760 patent of any "therapeutically effective amount" provided as a mass of extract per number of lymphocytes. Neither is the particular range recited in the instant claims 3 and 14 of more than 1 μg per 10^6 lymphocytes disclosed or suggested in the '760 patent.

Furthermore, there is no motivation set forth on the record to provide a therapeutically effective amount described as a mass of extract per number of lymphocytes, or to provide an amount of extract in the range of 1 μg or more per 10^6 lymphocytes. The Examiner has not cited any reference nor provided any sound reasoning as to why one or ordinary skill in the art who reads the '760 patent would think to either apply the extract to lymphocytes to enhance LAK activity or that a concentration of extract of 1 μg or more per 10^6 lymphocytes would be effective to increase LAK activity of lymphocytes.

As the '760 patent does not disclose or suggest modifications of its teachings to make each feature of claims 3 and 14, and the record does not explain any motivation to modify the teachings of the '760 patent to make the claimed invention, the Examiner has failed to properly establish *prima facie* obviousness of claims 3 and 14 over the '760 patent. Accordingly, the standing rejection of claims 3 and 14 under 35 U.S.C. § 103(a) over the '760 patent must be reversed. Such favorable action is respectfully requested.

Group VI

Claim 19 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This raises the issue of whether the Examiner has properly established *prime facie*

obviousness of claim 19, directed to a method for treating cancer or a tumor by enhancing LAK activity by administering a therapeutically effective amount of an aqueous extract of mycelia of *Lentinus edodes* (Issue 9). Appellants submit that she has not.

The Examiner fails to establish prima facie obviousness of claim 19 in view of the recitations of "by enhancing LAK activity", "therapeutically effective amount" and "adding ... enzymes"

The Examiner fails to establish a proper case of *prima facie* obviousness of the invention as claimed in claim 19. In particular, there is no disclosure or suggestion of the specific modifications of the teachings of the '760 patent necessary to make the claimed invention. Also, the Examiner has not put on the record any motivation to modify the teachings of the '760 patent to make the claimed invention.

The claimed invention

Claim 19 recites:

> 19. A method for treating tumor and/or cancer ***by enhancing LAK activity***, which comprises administering ***a therapeutically effective amount of a LAK activity enhancer*** containing an extract of Lentinus edodes mycelium that has been extracted from a solid medium comprising bagasse as a base which contains Lentinus edodes mycelia and which is obtainable by the following steps:
>
> delignifying the solid medium;

adding water and one or more enzymes selected from the group consisting of cellulase, protease and glucosidase to the delignified solid medium;

crushing and grinding said delignified solid medium in the presence of said enzyme(s);

inactivating the enzyme(s); and

filtering the resulting suspension.

The disclosure of the '760 patent

The disclosure of the '760 patent regarding the making of an extract from mycelia of *Lentinus edodes* is at col. 2, line 61 to col. 3, line 20 and is set forth above. This disclosure includes that the enzymes active in digestion of the culture are cellulase, chitinase, glucosidase and protease in the "nutrient medium and the tissue-medium" (col. 3, lines 1-3). Furthermore, the '760 patent describes that the extract acts only upon cancerous cells (col. 2, line 43). The '760 patent discloses administration of the extract prepared as described to rats implanted with an ascites tumor cell line, with inhibition of proliferation of the tumor cells (col. 6). The '760 patent also discloses that the antitumor activity of the extract is related to the enzyme composition of the mycelia (col. 8, line 30-32).

Differences between the claimed invention and the disclosure of the '760 patent

The invention of claim 19 is distinct from what is disclosed in the '760 patent in several respects. First, claim 19 recites a method for treating cancers or tumors by enhancing

LAK activity. This is contrary to the teaching of the '760 patent that the extract disclosed therein acts only upon cancerous cells.

Second, claim 19 recites that the extract that is used is one made by a process that includes adding at least one enzyme that is a cellulase, a protease or a glucosidase to the digestion of the mycelial culture. As has been repeatedly explained above, the '760 patent discloses that the culture should be digested using the enzymes endogenous to the mycelia and expressly relates the obtaining of antitumor activity in the extract to performing the digestion with the enzymes of the mycelia.

The '760 patent does not disclose or suggest the specific modifications of its teachings necessary to make the invention of claim 19. First, there is no suggestion that the extract can be applied in a therapeutic amount to enhance LAK activity in any subject. To the degree the Examiner has relied upon an inherency theory to suggest this element of the claim, Appellants note that the previous rejection for anticipation based upon inherency has been withdrawn.

Second, there is no suggestion that the practitioner should add enzymes to the culture during the digestion. Indeed, there is express teaching in the '760 patent that such should <u>not</u> be done.

Furthermore, the Examiner has not established motivation to one of ordinary skill in the art to make any modification of the teachings of the '760 patent to make the invention of claim 19. As explained above, the Examiner has merely speculated, incorrectly, that the skilled artisan would be motivated to substitute exogenous enzymes for the enzymes endogenous to the culture during the digestion. In fact, the '760 patent expressly states that obtaining antitumor activity in the extract is related to the enzyme composition of the mycelia. Contrary to the allegation of the Examiner, this would motivate the skilled artisan not to add any exogenous enzymes to the culture.

Furthermore, the Examiner has not put on the record any reasons for motivating the skilled artisan to treat a tumor by enhancing LAK activity using the extract. Indeed the '760 patent also provide motivation to the contrary, expressly stating that the extract acts directly upon the tumor cells.

As two elements of *prima facie* obviousness are not established by the Examiner, the rejection of claim 19 under 35 U.S.C. § 103(a) over the '760 patent should be reversed.

IX. Summary

Claims 1-10 and 12-20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. The Examiner

has failed to properly establish *prima facie* obviousness of any of the pending claims over the reference, and the rejection should be reversed on this ground alone.

As to claim 20, a process for making an extract, the modification of the teaching of the reference that enzymes should be added to the digestion of the mycelial culture is neither disclosed nor suggested by the '760 patent. Indeed, there is disclosure in the '760 patent that urges against such modification. This disclosure of the '760 patent evidences that the Examiner's proffer of motivation to make that change is mere speculation.

Claims 1-9 are product by process claims that recite the same process steps as claim 20 and the above argument applies to these claims as well.

Claims 12-18 are directed to a method for enhancing LAK activity of lymphocytes. In this instance, the Board should note that the '760 patent only describes use of an extract to directly kill tumor cells. Lymphocytes as a type of cell, whether as killer of tumor cells or as tumor cells *per se*, are not even mentioned in the '760 patent. There is no disclosure whatsoever of the concept of LAK activity and certainly no hint of any extract having activity of enhancing LAK activity of lymphocytes. Thus, the '760 patent fails to describe or suggest

modifications of its teachings necessary to obtain every feature of the invention of claims 12-18.

Furthermore, the Examiner has not made any mention of any motivation, either from the '760 patent or from the state of the prior art, to apply any extract to lymphocytes to enhance their LAK activity.

Claims 3 and 14, dependent upon claims 1 and 12, respectively, include as a feature that a concentration of extract of "1 μg or more per 10^6 lymphocytes" (claim 3 and 14)) is a therapeutically effective amount for enhancing LAK activity of lymphocytes (claim 14). The '760 patent does not disclose or suggest that an extract should be administered at a concentration of any mass per number of lymphocytes. Neither does the '760 patent disclose nor suggest that the concentration should be more than 1 μg per 10^6 lymphocytes.

Furthermore, the Examiner has not stated on the record any source of motivation to modify the teachings of the '760 patent to arrive at the invention of claims 3 and 14.

Finally, claim 19 is directed to a method for treating cancers or tumors by enhancing LAK activity. This claim contains three modifications over the '760 patent that are neither disclosed nor suggested by the reference. In particular, the '760 patent expressly teaches that the extract acts directly on tumor cells. Thus, there is no teaching or

suggestion that a therapeutic amount of extract for enhancing LAK activity should be administered to a subject. Both the therapeutic amount and the enhancement of LAK activity are absent from the disclosure of the '760 patent. Also, the extract used in claim 19 is described as a product of a process, like that of claim 20, in which a culture of mycelia is digested in an aqueous medium containing added enzymes. Again, the '760 patent expressly urges that only the enzymes endogenous to the culture should be used for the digestion.

Furthermore, the Examiner has not put on the record any motivation to one of ordinary skill in the art to make these modifications in the face of the teachings of the '760 patent to the contrary.

Furthermore, there is evidence of record comparing the extract of the invention to the extracts characterized in the '760 patent. Claim 20 is a process of making an extract and claims 1-9 are directed to the extract as a product of the process. The evidence comparing the extract obtained by the process of claim 20 shows that it is substantially different from the LAP, LAP-1 and LAP-2 extracts prepared in the '760 patent. Evidence of differences in the major sugar component between the extract of the invention and the LAP-1 and LAP-2 extracts of the '760 patent has been accepted by the Examiner as

sufficient to overcome a rejection of composition claims based upon inherency.

The Examiner has admitted on the record that the extract of the invention would be expected by one of skill in the art to be identical to that of the '760 patent, because the processes for making the extracts are similar. The Examiner has used this expectation as a basis for a rejection for lack of novelty based upon inherency. Therefore, differences in the products obtained by the process described in the instant claims and the products described in the '760 patent must be considered unexpected by the skilled artisan.

Appellants submit that the evidence of differences in the products of the invention and in the products described in the '760 patent are an unexpected result sufficient to rebut any case of *prima facie* obviousness of claims 1-9 and 20 deemed properly established by the Examiner. The rejection of claims 1-9 and/or 20 under 35 U.S.C. § 103(a) over the '760 patent may be reversed for this reason also.

Claim 10 is a method of using the product of claim 1. If claim 1 is found allowable, claim 10, being a method of use commensurate in scope with an allowable product claim, should also be found allowable.

The standing rejection of at least claims 1-10 also fails as a matter of law. *Prima facie* obviousness is a legal theory

that assigns the burden of proof. Upon establishment by the Examiner of *prima facie* obviousness of the claimed invention, the Applicant (Appellant) must present evidence sufficient to rebut the Examiner's case of obviousness to establish that the claims are patentable.

In the present case, the Examiner has accepted the comparative evidence of record as sufficient to overcome a rejection of claims 1, 2 and 4-11 for lack of novelty based upon a theory of inherency. Thus, the comparative evidence of record has been found sufficient to rebut a presumption of identity, the epitome of obviousness. To then maintain or impose a rejection of claims 1-10 based upon obviousness is legally untenable.

X. Conclusion

The rejection of claims 1-10 and 12-20 under 103(a) over the '760 patent fails and must be reversed as to all of the pending claims because the Examiner has not properly established *prima facie* obviousness of the claimed invention.

As to claims 1-9 and 20, Appellants have also presented evidence of record sufficient to rebut any allegation of *prima facie* obviousness that the Examiner may be deemed to have properly established. This is an additional reason to reverse the rejection as to these claims.

As to claims 1-10, the standing rejection may be found improper as a result of the operation of law. Evidence found sufficient to rebut a presumption of identity based upon inherency over a reference should also be found sufficient to rebut an allegation of *prima facie* obviousness over the same reference.

The favorable action by the Board of reversal of the rejection of claims 1-10 and 12-20 under 103(a) as being unpatentable over the '760 patent, and an order to the Examiner to allow these claims is respectfully requested.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a five (5) month extension of time for filing a response in connection with the present application. An extension of two (2) month(s) for responding to the Final Rejection was previously requested and paid for on October 17, 2003. Thus a fee of $1,590.00 is required to obtain an additional three (3) month(s) for filing the Notice of Appeal.

The required total fee of $1,920.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: APPENDIX

XI. Appendix - Claims on Appeal

1. (previously presented) A LAK activity enhancer containing an extract of Lentinus edodes mycelium, which is prepared by

preparing a suspension by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more additive enzymes selected from the group consisting of cellulase, protease and glucosidase, wherein the solid medium is based on bagasse and defatted rice bran; and

raising the temperature of the suspension to about 80-100°C to inactivate the enzymes.

2. (original) The LAK activity enhancer of claim 1 for enhancing LAK activity by acting on lymphocytes derived from peripheral blood.

3. (original) The LAK activity enhancer of claim 2 containing an extract of Lentinus edodes mycelium at a concentration of 1 μg or more per 10^6 lymphocytes.

4. (original) An LAK activity-enhancing formulation containing the LAK activity enhancer of claim 1.

5. (original) A pharmaceutical or veterinary LAK activity-enhancing formulating comprising the LAK activity enhancer of claim 1 and pharmaceutically acceptable carrier.

6. (original) The LAK activity-enhancing formulation of claim 4 or 5 for oral administration.

7. (original) The LAK activity-enhancing formulation of claim 4 in the form of a food, drink or feed.

8. (original) The LAK activity-enhancing formulation of claim 4 or 5 for injection or percutaneous administration.

9. (previously presented) The LAK activity-enhancing formulation of claim 4, wherein said formulation is used for treating tumor and/or cancer.

10. (previously presented) A method for treating tumor and/or cancer comprising administering an effective amount of the LAK activity-enhancing formulation of claim 4.

12. (previously presented) A method for enhancing LAK activity which comprises administering to a mammal a therapeutically effective amount of LAK activity enhancer

containing an extract of Lentinus edodes mycelium, which is prepared by:

preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase, wherein said solid medium is based on bagasse and defatted rice bran; and

raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).

13. (previously presented) The method of claim 12 wherein said LAK activity enhancer acts on lymphocytes derived from peripheral blood.

14. (previously presented) The method of claim 12 wherein said LAK activity enhancer contains an extract of Lentinus edodes mycelium at a concentration of 1 μg or more per 10^6 lymphocytes.

15. (previously presented) The method of claim 12 wherein said LAK activity enhancer further comprises a pharmaceutically acceptable carrier.

16. (previously presented) The method of claim 12 wherein said LAK activity enhancer is orally administered.

17. (previously presented) The method of claim 12 wherein said LAK activity enhancer is in the form of a food, drink or feed.

18. (previously presented) The method of claim 12 wherein said LAK activity enhancer is administered by injection or a percutaneous route.

19. (previously presented) A method for treating tumor and/or cancer by enhancing LAK activity, which comprises administering a therapeutically effective amount of a LAK activity enhancer containing an extract of Lentinus edodes mycelium that has been extracted from a solid medium comprising bagasse as a base which contains Lentinus edodes mycelia and which is obtainable by the following steps:

delignifying the solid medium;

adding water and one or more enzymes selected from the group consisting of cellulase, protease and glucosidase to the delignified solid medium;

crushing and grinding said delignified solid medium in the presence of said enzyme(s);

inactivating the enzyme(s); and

filtering the resulting suspension.

20. (previously presented) A method of preparing a LAK activity enhancer which comprises

preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase, wherein said solid medium is based on bagasse and defatted rice bran; and

raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).

COPY

PATENT
0230-0161P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Kenji ASANO et al.

Appl. No.: 09/856,718

Filed: January 28, 2002

Conf.: 3333

For: LAK ACTIVITY ENHANCERS DERIVED FROM EXTRACT OF LENTINUS EDODES MYCELIUM AND LAK ACTIVITY-ENHANCING FORMULATIONS CONTAINING THE EXTRACT

Before the Board of Appeals

Appeal No:

Group: 1654

Examiner: COE, S.D.

A P P E A L B R I E F

January 20, 2004
(Tuesday after holiday)

PATENT
0230-0161P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Kenji ASANO et al.	Conf.:	3333
Appl. No.:	09/856,718	Group:	1654
Filed:	January 28, 2002	Examiner:	COE, S.D.

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BRIEF ON BEHALF OF APPELLANT

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APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

January 20, 2004
(Tuesday after holiday)

Sir:

In response to the Examiner's Office Actions dated December 17, 2002, and the Advisory Actions dated October 1, 2003 and December 11, 2003, the following Appeal Brief is respectfully submitted in connection with the above-identified application.

I. Real Party in Interest

The present application is a National Stage application of International Application PCT JP99/06616. The "Applicant" of the International Appplication is Kobayashi Pharmaceutical Company, Ltd. of Osaka, Japan. No Assignment of the present application from the inventors Kenji Asano, Yukiko Matsuda and Yutaka Tajima to Kobayashi Pharmaceutical Company, Ltd. has yet been recorded in the USPTO.

II. Related Appeals and Interferences

No appeal or interference involving a related application is known to Applicants' Representative.

III. Status of the Claims

Claims 1-10 and 12-20 are pending. Claim 11 has been canceled.

Claims 1-10 and 12-20 stand rejected under 35 U.S.C. § 103(a) over U.S. Patent 4,461,760. The decision of the Examiner in the Advisory Action of October 1, 2003 to maintain this rejection is appealed.

The text of the appealed claims is provided as Appendix I attached hereto.

IV. Status of Amendments

A Reply Under 37 CFR 1.116 was filed on April 17, 2003. The Advisory Action of October 1, 2003, indicates that the Amendment was entered.

A second Reply under 37 CFR 1.116 was filed on October 17, 2003. That paper suggested no amendments to the claims, but its arguments were considered by the Examiner but deemed not to overcome the remaining rejection as indicated in the Advisory Action of December 11, 2003.

V. Summary of the Invention

Treatment of peripheral lymphocytes with certain compounds, for example interleukin-2, produces an activated, heterogeneous population of cells called, "lymphokine activated killer cells" or "LAK" cells (paragraph bridging pp. 2-3). One embodiment of the present invention is a composition having the biological activity of producing LAK cells when used to treat peripheral lymphocytes, or of increasing the anti-tumor activity of LAK cells (p. 7, lines 1-4). The composition comprises an extract of *Lentinus edodes* mycelia (p. 7, lines 19-20). In general, the extract is prepared by crushing and delignifying a culture of *Lentinus edodes* mycelia in the presence of water and added enzymes (p. 10, lines 19-24). The extract can be formulated for pharamaceutical or veterinary use and for different routes of

administration, including injection or oral administration, or as a food additive (p. 8, lines 6-16).

For activation of peripheral lymphocytes, the composition of the invention is typically added to the lymphocytes such that 1 µg to 1 mg of the extract is provided to 10^6 lymphocytes (p. 12, line 22).

Another embodiment of the invention is use of the composition to enhance LAK activity of lymphocytes by either contacting peripheral lymphocytes or LAK cells with the composition in culture (p. 12, lines 5-29) or by injection into a subject (p. 13, line 1-5). LAK cells treated with the composition may be reinfused into a subject for immunotherapy (p. 12, line 10). Treatment can be for generalized improvement of immune function or for treatment of cancers (p. 8, lines 17-28). Treatment of tumors is not direct, but is mediated by the induction of LAK cell activity in the patient (p. 8, lines 20-21).

VI. Issues for review by the Board

Appellants submit that the rejection of claims 1-10 and 12-20 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 4,461,760 ("the '760 patent") raises the following issues for consideration by the Board of Appeals:

1. Does the Examiner correctly establish *prima facie* obviousness of claim 20, directed to a process comprising crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

2. If the Examiner has properly established *prima facie* obviousness of the invention of claim 20, is there evidence of record sufficient to rebut *prima facie* obviousness?

3. Once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes, is an obviousness rejection of the claims over the same reference legally tenable?

4. Does the Examiner correctly establish *prima facie* obviousness of claims 1-9, directed to a composition that is prepared by a process of crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

5. If the Examiner has properly established *prima facie* obviousness of the invention of claims 1-9, is there evidence of record sufficient to rebut *prima facie* obviousness?

6. Is claim 10, directed to a method for treating cancer or tumors by administering a formulation of claim 1, allowable if claim 1 is unobvious?

7. Does the Examiner properly establish *prima facie* obviousness of claims 12-18, directed to methods for enhancement of LAK activity in lymphocytes, over the disclosure of the '760 patent?

8. Does the Examiner properly establish *prima facie* obviousness of claims 3 and 14, which recite a range of 1 μg or more of an extract of *Lentinus edodes* per 10^6 lymphocytes, over the disclosure of the '760 patent?

9. Does the Examiner properly establish *prima facie* obviousness of claim 19, directed to a method for treating cancer by enhancing LAK activity by administering a composition that is prepared by a process of crushing mycelia and cultured medium of *Lentinus edodes* in water in the presence of added enzymes, over the disclosure of the '760 patent?

VII. Grouping of the claims

Appellants submit that the following groups of claims raise separate issues for consideration by the Board of Appeals.

Group I, claim 20, raises issues 1 and 2 for consideration.

Group II, claims 1-9, raises issues 3, 4 and 5 for consideration.

Group III, claim 10, raises issue 6 for consideration.

Group IV, claims 12-18, raises issue 7 for consideration.

Group V, claims 3 and 14, raises issue 8 in addition to issues 3-5 for consideration.

Group VI, claim 19, raises issue 9 for consideration.

VIII. Argument

Group I

Claim 20 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the '760 patent. This rejection raises for consideration by the Board the questions of whether the Examiner has properly established *prima facie* obviousness of the invention (Issue 1). If the Board determines that the Examiner has properly established *prima facie* obviousness of the invention, the Board must then go on to consider whether there is any evidence of record that establishes unobviousness of the invention (Issue 2).

The Examiner fails to establish proper prima facie obviousness of the process described by claim 20

The Examiner bears the initial burden of establishing *prima facie* obviousness of the claimed invention. The claim is granted to the Applicant (Appellant) if the Examiner fails to meet this initial burden. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). For the Examiner to establish a proper case of *prima facie* obviousness, the references cited must describe or suggest any specific modification of the reference, no matter

how minor, to obtain the invention from the disclosure of the reference. *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1324 (Fed. Cir. 1991). There must also be motivation, provided by the reference itself or by the state of the art at the time the invention was made, to so modify the teachings of the reference to obtain the invention. *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999). Motivation to modify the teachings of the reference must be found even if, as in the present case, only a single reference is cited in making the rejection. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 37 USPQ2d 1314, 1318 (Fed. Cir. 1996). Appellants submit that both of these elements of *prima facie* obviousness are absent from the standing rejection.

The claimed invention

Claim 20 recites:

> A method of preparing a LAK activity enhancer which comprises
>
> preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of ***additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase***, wherein said solid medium is based on bagasse and defatted rice bran; and
>
> raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s). (Emphasis added.)

The teachings of the '760 patent

The portion of the '760 patent that describes extraction of mycelia of *Lentinus edodes* is found at col. 2, line 61 to col. 3, line 20 and reads as follows:

> The crushed medium (the mixture of mycelium and the medium, which is called the nutrient medium and tissue-medium hereinafter) was packed in a tank, and after adding 5 liters of water at pH 3 to 8 per 800 grams of the nutrient medium and tissue-medium, it was blended and stirred stepwise for a given period of time: that is the temperature was changed in the range from 40° C. to 60° C. depending on pH for promoting enzymation ***according to activities of enzymes such as cellulase, chitinase, glucosidase and protease existing in the nutrient medium and tissue-medium***. Finally it was blended and stirred at 80° C. for deactivating the enzymes, and in this step the mycelial components, the metabolites of mycelia, and cellulose decomposition products of the medium component were dissolved in water.
>
> The suspension thus obtained was packed in a filtering bag of flannel, and compressed to filter, and the filtrate was further filtered through a membrane filter and sterilized to obtain an extracted solution.
>
> The extracted solution thus obtained was freeze-dried and a powder (which is called as LEM hereinafter) was obtained. To the aqueous solution of LEM, ethyl alcohol of 4-fold volume of the LEM solution was added, and the precipitate produced was washed with 80% ethyl alcohol twice, and then centrifuged and freeze-dried to obtain a powder (which is called as LAP hereinafter). (Emphasis added.)

The '760 patent discloses that the extract so produced has antitumor activity (*e.g.* col. 2, line 43). Important to the instant question, the '760 patent discloses (at col. 8, lines 27-32) that the antitumor activity is found in a fraction that is,

> ...mainly composed of xylose, as described above, and also had considerable amounts of glucose, galactose,

> mannose and arabinose. These results clearly reflected the polysaccharide composition of the medium, and the fact that xylose is the main sugar in place of glucose strongly suggests the relation with the activity of the enzyme of mycelia of C. shiitake.

The differences between the invention and the teachings of the reference

During prosecution to date, Appellants have argued that the present claim 20 includes addition of one or more cellulase, protease or glucosidase enzymes to the crushed mycelia and medium composition to digest the mixture. On the other hand, the '760 patent teaches that the mycelia and the medium are to be decomposed solely (after the crushing) by the action of enzymes as are originally present in the cells or the medium. (Note the text highlighted above.)

The Examiner takes a position that the addition of the enzymes is obvious. She argues that the substitution of exogenous enzymes for the endogenous enzymes would be routine, as the enzymes are merely added for their known purpose of digesting the culture medium and cells and that the knowledge of the skilled artisan that such is the activity of these enzymes provides the requisite motivation.

Appellants disagree. First, the claimed invention is not a mere substitution of exogenous enzymes for endogenous ones. Rather, as described in claim 20, it is addition of exogenous enzymes. Nothing is done to inactivate or remove the endogenous

enzymes. The '760 patent clearly states that enzymes "existing in the nutrient medium and tissue-medium" are sufficient to digest the culture. There is no suggestion whatsoever that any advantage is obtained by altering the enzyme content of the culture during the digestion process. Indeed, the '760 patent expressly describes that the antitumor activity of the extract is related to the enzyme composition of the mycelia of the mushroom. Therefore, the '760 patent in fact strongly suggests that the enzyme content of the digestion should not be altered.

Appellants note that there is no characterization in the '760 patent of the particulars of the enzymes produced during the culturing, other than to say that the pH of the digestion must be optimized, and therefore the relative amounts of chitinase, cellulase, protease and glucosidase activities are unknown. Also unknown is the nature of the antitumor component that is obtained from the extract. Appellants submit that the scientific method is characterized by controlling variables, so as to minimize changes between experiments. Thus, the skilled biochemist, rather than being motivated to alter the uncharacterized mixture of the digesting culture by increasing the activity of any enzyme during the digestion, would be motivated to leave it be, so as to avoid inadvertantly inactivating the (also uncharacterized) antitumor component obtained in the extract. Such conservatism is indeed justified

in view of the express teaching of the '760 patent that the endogenous enzyme composition is important to obtaining an antitumor activity in the resulting extract. It seems the Examiner has substituted her own thinking for that of the artisan of ordinary skill to allege motivation.

Thus one can see that the '760 patent fails to describe or suggest at least one modifications of its teachings that are features of the instant claim 20, the addition of enzymes to the culture during digestion. In fact, the '760 patent expressly urges against this. One can also see that the Examiner's allegation of motivation fails in that her speculation regarding motivation is contrary to an express teaching of the '760 patent.

Accordingly, two elements of a proper *prima facie* case of obviousness are absent from the rejection of claim 20 under 35 U.S.C. § 103(a) over the '760 patent. Therefore this rejection must be reversed.

There is evidence of record of differences between the extract resulting from the process of claim 20 and the extracts disclosed by the '760 patent and this is unexpected and sufficient to rebut prima facie obviousness

If the Board should agree that the Examiner has properly established *prima facie* obviousness of claim 20, the Board must then consider whether there is evidence of record sufficient to rebut that conclusion. Appellants submit that there is evidence

in the record that the process of claim 20 provides a composition that is distinct from the composition of the extracts characterized in the '760 patent. Appellants submit that this is an unexpected result and sufficient evidence to rebut *prima facie* obviousness.

An exemplary extract obtained by the process of claim 20 is described in Example 1 of the specification and is characterized as to chemical content at p. 21, line 25 to p. 22, line 7. There the extract is described as being composed of 25.3% carbohydrate, 19.7% protein, 2.6% polyphenols, 8% crude fat, 22% crude ash and about 20% soluble nitrogen-free materials other than carbohydrate. These last four amounts might be summed as 52.6% "other".

Furthermore, the carbohydrate component is further analyzed as being 15.2% xylose, 8.2% arabinose, 8.4% mannose, 39.4% gulose[1], 5.4% galactose, 12.0% N-acetylglucosamine and 11.3% glucuronic acid.

The comparable extract in the '760 patent is designated "LEM", or "LAP" after alcohol precipitation and lyophilization. LAP is characterized in Table 1 at col. 3 as being composed of 24.8% (248 µg/mg) protein, 57.6% sugar and 17.6% (other). While the carbohydrate contents are not analyzed for the same sugars

[1] The specification indicates "Gul". It is not entirely clear to Appellants' Representative if this is to represent "gulose" or is a typographical error and Glu, for "glucose" is intended. If the latter, the Board might note that the LAP extract contains 19.9% glucose.

entirely, the xylose content is 30.2%, the galactose content is 20.3%, the arabinose content is 17.4% and the mannose content is 9.5%. At least these sugars are greatly different in their amounts and proportions compared to the extract obtained by the process of claim 20.

Furthermore, the Examiner has asserted during prosecution that the composition of claims 1, 2 and 4-10 was inherently the same as the product of the process described in the '760 patent. In the response of September 30, 2002, Appellants pointed out that the product of the process as described in claim 1, which recites the same steps as the process of claim 20, comprises approximately 40% glucose[2]. On the other hand, the LAP-1 and LAP-2 compositions of the '760 patent, which are chromatographic fractions of LAP, comprise 39.0% and 30.4% xylose, respectively. The Examiner accepted this evidence of distinction between the composition of the present invention and that produced by the process of the '760 patent and withdrew the rejection under 35 U.S.C. § 102.

Appellants submit that presentation of an anticipation rejection based upon inherency constitutes an admission by the Examiner that the expectation of the one of skilled in the art is that the modification of the process of the '760 patent by the addition of one or more of cellulase, protease and

[2] This may be in error, in that, as noted above, the specification indicates "Gul".

glucosidase would result in the same product. Therefore, finding differences between the extract made by the process of claim 20 and that obtained by the process of the prior art must therefore be a result obtained by the process of claim 20 that is unexpected by the artisan of ordinary skill.

Appellants submit that, even if the Board should hold that the Examiner has established *prima facie* obviousness of the process of claim 20 in view of the '760 patent, the differences overall composition, and especially in distribution of carbohydrate among different sugars between the extract prepared in Example 1 of the instant application and the LAP extract described in the '760 patent, are sufficient evidence of unobviousness to rebut the Examiner's assertion. Accordingly, the rejection of claim 20 under 35 U.S.C. § 103(a) as unpatentable over the '760 patent may also be reversed on this basis and Appellants respectfully request such favorable action.

Group II

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This rejection raises for consideration by the Board the issue of whether once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes, a

rejection of the claims over the same reference is legally tenable (Issue 3). If so, then this rejection also raises the issue of whether the Examiner has properly established *prima facie* obviousness of the claimed extract (Issue 4). If the Board determines that *prima facie* obviousness is indeed established, then they must consider whether there is evidence of record sufficient to establish unobviousness of the invention (Issue 5).

Once a rejection for anticipation based upon inherency of the identity of the products of similar processes has been overcome by evidence of differences between the products of the two processes an obviousness rejection of the claims over the same reference is not legally tenable

The present claim 1 recites:

> 1. A LAK activity enhancer containing an extract of Lentinus edodes mycelium, which is prepared by preparing a suspension by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more ***additive enzymes selected from the group consisting of cellulase, protease and glucosidase,*** wherein the solid medium is based on bagasse and defatted rice bran; and raising the temperature of the suspension to about 80-100°C to inactivate the enzymes. (Emphasis added.)

Claims 2-9 are dependent ultimately from claim 1.

Thus, claims 1-9 are "product-by-process" claims.

Typically, patentability of product-by-process claims is evaluated without reference to the specific process steps. When an Examiner provides a reference that discloses a product of a closely similar process, the Examiner can properly take a

position that a product of that process is expected to be the same as the claimed product in support of a rejection for anticipation based upon inherency. The burden of persuasion then shifts to the Applicant (Appellant) to show by a preponderance of the evidence that the claimed product is different. *In re Fitzgerald,* 205 USPQ 594 (CCPA 1980).

Such has been the course of prosecution of claims 1, 2 and 4-10 to this point, but the Examiner now makes an obviousness rejection (of claims 1-10) over the same single reference used to assert anticipation. This cannot be a proper rejection.

Prima facie obviousness is a legal theory that shifts the burden of proof. The Examiner bears an initial burden of establishing obviousness of the invention by the preponderance of the evidence. When the Examiner establishes *prima facie* obviousness, the burden of persuasion shifts to the Applicant (Appellant) to rebut the conclusion of obviousness by evidence establishing unobviousness of the invention. *In re Piasecki,* 223 USPQ 785 (Fed. Cir. 1984). Evidence of a result of the invention not expected by the artisan of ordinary skill is typically sufficient. *In re Soni,* 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), *In re Mayne,* 42 USPQ2d 1451, 1454 (Fed. Cir. 1997).

Making a rejection for anticipation based upon inherency represents a conclusion by the Examiner that identity of the products of the process described by the reference and of the

process described in the claim is the expectation of the skilled artisan. Overcoming of the rejection based upon inherency by evidence of differences between the products establishes the sufficiency of the evidence to show a result not expected by one of ordinary skill in the art. By withdrawing the rejection, the Examiner admits the evidence has been found sufficient to rebut a presumption of anticipation, the epitome of obviousness (*Jones v. Hardy*, 220 USPQ 1021 (Fed. Cir. 1984)), and therefore must also be sufficient to rebut any rejection for obviousness over the same reference.

In such an instance making or maintaining a rejection under 35 U.S.C. § 103(a) based upon the same reference is therefore not legally supportable.

As explained above, Appellants have overcome a rejection of claims 1, 2 and 4-11 for anticipation over the '760 patent based upon inherency. (See paragraph 5 of the Office Action of December 17, 2002, Appellants' reply of April 17, 2003 and the Advisory Action of October 1, 2003, advising that the rejection under 35 U.S.C. § 102 had been overcome by Appellants' response.) The rejection was overcome by explaining and providing evidence from the respective specifications of differences between the product-by-process of claim 1 and the product obtained by the process of the '760 patent.[3] These

[3] Thus, the facts of the present application distinguish it from the case of *Fitzgerald, supra*.

differences in composition are explained in detail above and the Examiner found them to be sufficient evidence to rebut her presumption of identity. Appellants submit that the evidence of differences must therefore also be sufficient to establish unobviousness of the product claimed in claim 1 over the product of the '760 reference. The standing rejection of claims 1-9 as being obvious over the '760 reference should therefore fail by operation of law.

The Examiner fails to establish proper prima facie obviousness of the extract described by claims 1-9

The '760 patent does not disclose or suggest each and every specific modification of its teachings to obtain the invention of claims 1-9. Neither is there any motivation to modify what is taught by the '760 patent to arrive at the invention described by claims 1-9.

As explained in detail with respect to claim 20, the '760 patent fails to disclose or suggest that an extract of *Lentinus edodes* mycelia should be made by a process that includes a step of digesting a culture of the mycelia with added enzymes selected from at least one of cellulases, proteases and glucosidases. There is no disclosure or suggestion that any enzymes not already present in the culture should be added.

Also, the Examiner fails to provide any sufficient allegation of motivation to modify the teachings of the '760

patent to achieve the invention of claims 1-9. The Examiner has not provided any evidence or sound reasoning of motivation, but has merely speculated, incorrectly, that a skilled biochemist would make the modification suggested by the Examiner. Therefore, the Examiner has failed to properly establish *prima facie* obviousness of the claimed invention. Accordingly, the standing rejection of claims 1-9 under 35 U.S.C. § 103(a) over the '760 patent should be reversed.

There is evidence of record that composition of the extract is unexpectedly different from the extract of the '760 patent

Furthermore, as explained above, there is evidence of record that the process steps recited in claim 1 and the process described in the '760 patent result in differenT compositions of the extract that is obtained.

Again, an exemplary extract obtained by the process of claim is described in Example 1 of the specification and is characterized as to chemical content at p. 21, line 25 to p. 22, line 7. The extract product according to the instant claim 1 is shown by comparison of these descriptions to have a different proportion of protein, carbohydrate and "other substances" from the LAP composition of the '760 patent. Furthermore, to the degree the carbohydrates of each extract are characterized, the proportion of different sugars in the claimed extract is

substantially different from the LAP, LAP-1 and LAP-2 preparations of the '760 patent.

The Examiner has admitted by her presentation of an inherency rejection that one of ordinary skill in the art would expect the composition of claim 1 to be identical to the composition of the '760 patent. Therefore, differences in the compositions must be taken as a result that would be unexpected by one of skill in the art who reads the '760 patent.

Therefore, there is evidence of record sufficient to establish an unobvious distinction between the product of the instant claim 1 and the product described in the '760 patent. Accordingly, the rejection of claims 1-9 under 35 U.S.C. § 103(a) over the '760 patent may be reversed on this basis as well. Appellants respectfully request such favorable action.

Group III

Claim 10 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This rejection raises the issue of whether claim 10, directed to a method for treating cancer or tumors, must be considered unobvious over the '760 patent if claim 1 is considered unobvious over the '760 patent (Issue 6).

Unobviousness of claim 1 establishes unobviousness of claim 10

Appellants submit that, should the Board find claim 1 unobvious, then claim 10 must also be deemed unobvious.

Claim 10 recites:

> 10. A method for treating tumor and/or cancer comprising administering an effective amount of the LAK activity-enhancing formulation of claim 4.

Claim 4 is dependent upon claim 1, and therefore claim 10 is a method of use of the "product-by-process" described by claim 1.

For all of the reasons described above, Appellants have established that the product that is administered in the method of claim 10 is not obvious over the '760 patent and claim 1 is therefore allowable over the reference. Claim 10 is commensurate in scope with the product claim asserted by Appellants to be allowable. Accordingly, claim 10 should also be found patentable over the '760 patent. M.P.E.P. 821.04.

Group IV

Claims 12-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 reference. This rejection raises the issue of whether the Examiner has properly established *prima facie* obviousness of the invention described in claims 12-18 (Issue 7).

The Examiner does not properly establish prima facie obviousness of the methods of claims 12-18 over the disclosure of the '760 patent

Appellants submit that the Examiner has failed to establish proper *prima facie* obviousness of the invention of claims 12-18 over the disclosure of the '760 patent. In particular, the reference fails to disclose or suggest one or more specific modifications of its teachings to make the claimed invention. Furthermore, there is no motivation put forth on the record to modify the teachings of the '760 patent to obtain the invention that is described by claims 12-18.

The claimed invention

Claim 12 recites:

> 12. A method for ***enhancing LAK activity*** which comprises administering to a mammal ***a therapeutically effective amount of LAK activity enhancer*** containing an extract of Lentinus edodes mycelium, which is prepared by:
>
> preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and ***one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase***, wherein said solid medium is based on bagasse and defatted rice bran; and
>
> raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).

Claims 13-18 depend from claim 12.

The teachings of the '760 patent

The '760 patent describes an extract of *Lentinus edodes* that is applied directly to tumor cells for its tumor cell-killing activity. For example, at col. 2, line 43, the '760 patent describes that the extract, "acts only upon cancerous cells". Furthermore, in the working Examples experiments measuring the proliferation of ascities tumor cells *in vivo* are performed. See, (G) at col. 6. There is no description at all of any experiments using lymphocytes or any blood or immune cell.

Differences between the invention and the '760 patent

As emphasized in the text of claim 12 above, the instant invention is a method for enhancing LAK cell activity. The method has as one of its results an effect of tumor killing. However, the claimed method is more general; it can be applied for general enhancement of immune function. *See*, p. 8, lines 17-24. The instant specification makes quite clear that the extract of the present invention does not specifically attack tumor cells. *See*, p. 8, lines 20-21. This is reflected in claim 12, which recites a method for enhancing LAK activity.

Furthermore, the instant claim 12 recites that the extract to be applied is one prepared by a process that includes adding one or more enzymes that is a cellulase, a protease or a

glucosidase to a digestion of a culture of *Lentinus edodes* mycelia. As has been explained in detail above, this process for producing the extract is not described in the '760 patent. Neither is there any suggestion made to modify the process that is described in the '760 patent to make such an extract.

Finally, the instant claim 12 recites that a "therapeutically effective amount of LAK activity enhancer" is administered. The '760 patent makes no disclosure or suggestion of what might be a therapeutically effective amount of a LAK activity enhancer might be. Of course, the '760 patent cannot include such disclosure or suggestion, as the '760 patent is all about an extract that acts upon tumor cells, not upon lymphocytes.

As there is no disclosure or suggestion in the '760 patent of any of the above differences between the invention and the teachings of the reference, it is plain that the specific modifications of the disclosure of the '760 patent to make the claimed invention are not taught or suggested by the reference.

Furthermore, the Examiner has never set forth on the record any kind of motivation to produce an extract for purposes of enhancing LAK activity. The Examiner has not mentioned any reason, put forward by a reference or by any reasoned statement of the Examiner, to develop any method for enhancing LAK

activity of lymphocytes, and especially for developing any such method using an extract of *Lentinus edodes*.

As the '760 patent fails to disclose or suggest specific modifications of its disclosure to obtain every feature of the instant claims 12-18, and the record does not contain any motivation to modify the teachings of the '760 patent to make the present invention, the Examiner fails to establish a proper *prima facie* case of obviousness of claims 12-18 over the '760 patent. Accordingly, the rejection of claims 12-18 under 35 U.S.C. § 103(a) over the '760 patent should be reversed and such favorable action is respectfully requested.

Group V

Claims 3 and 14, dependent upon claims 1 and 12, respectively, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. Claims 3 and 14 recite as a feature in addition to those of claims 1 and 12 that the amount of the extract in the composition (claim 3) or applied in the method (claim 14) is "at a concentration of 1 μg or more per 10^6 lymphocytes".

Appellants submit that the instant rejection raises for consideration by the Board the issue of whether the Examiner properly establishes *prima facie* obviousness of claims 3 and 14, which recite a range of 1 μg or more of an extract of *Lentinus*

edodes per 10^6 lymphocytes, over the disclosure of the '760 patent (Issue 8). Appellants submit that she has not.

The Examiner does not properly establish prima facie obviousness of claims 3 and 14 over the disclosure of the '760 patent, in view of their recitation of the range of 1 μg or more of an extract of Lentinus edodes per 10^6 lymphocytes

The invention described in the instant claim 14 is a method for enhancing LAK activity of lymphocytes. Claim 12, from which claim 14 depends, describes administering a "therapeutically effective" amount of an extract of *Lentinus edodes* to achieve this. Claims 3 and 14 recite a particular dosage range that is described as a mass of the extract per number of lymphocytes. That is, a "therapeutically effective amount" is described in claims 3 and 14 as "at a concentration of 1 μg or more per 10^6 lymphocytes".

On the other hand, the '760 patent describes use of an extract of *Lentinus edodes*, which is established above to be substantially different from the extract applied in the present invention, to directly kill tumor cells. There is no description or suggestion in the '760 patent of any "therapeutically effective amount" provided as a mass of extract per number of lymphocytes. Neither is the particular range recited in the instant claims 3 and 14 of more than 1 μg per 10^6 lymphocytes disclosed or suggested in the '760 patent.

Furthermore, there is no motivation set forth on the record to provide a therapeutically effective amount described as a mass of extract per number of lymphocytes, or to provide an amount of extract in the range of 1 μg or more per 10^6 lymphocytes. The Examiner has not cited any reference nor provided any sound reasoning as to why one or ordinary skill in the art who reads the '760 patent would think to either apply the extract to lymphocytes to enhance LAK activity or that a concentration of extract of 1 μg or more per 10^6 lymphocytes would be effective to increase LAK activity of lymphocytes.

As the '760 patent does not disclose or suggest modifications of its teachings to make each feature of claims 3 and 14, and the record does not explain any motivation to modify the teachings of the '760 patent to make the claimed invention, the Examiner has failed to properly establish *prima facie* obviousness of claims 3 and 14 over the '760 patent. Accordingly, the standing rejection of claims 3 and 14 under 35 U.S.C. § 103(a) over the '760 patent must be reversed. Such favorable action is respectfully requested.

Group VI

Claim 19 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. This raises the issue of whether the Examiner has properly established *prime facie*

obviousness of claim 19, directed to a method for treating cancer or a tumor by enhancing LAK activity by administering a therapeutically effective amount of an aqueous extract of mycelia of *Lentinus edodes* (Issue 9). Appellants submit that she has not.

The Examiner fails to establish prima facie obviousness of claim 19 in view of the recitations of "by enhancing LAK activity", "therapeutically effective amount" and "adding ... enzymes"

The Examiner fails to establish a proper case of *prima facie* obviousness of the invention as claimed in claim 19. In particular, there is no disclosure or suggestion of the specific modifications of the teachings of the '760 patent necessary to make the claimed invention. Also, the Examiner has not put on the record any motivation to modify the teachings of the '760 patent to make the claimed invention.

The claimed invention

Claim 19 recites:

> 19. A method for treating tumor and/or cancer ***by enhancing LAK activity***, which comprises administering ***a therapeutically effective amount of a LAK activity enhancer*** containing an extract of Lentinus edodes mycelium that has been extracted from a solid medium comprising bagasse as a base which contains Lentinus edodes mycelia and which is obtainable by the following steps:
>
> delignifying the solid medium;

adding water and one or more enzymes selected from the group consisting of cellulase, protease and glucosidase to the delignified solid medium;
crushing and grinding said delignified solid medium in the presence of said enzyme(s);
inactivating the enzyme(s); and
filtering the resulting suspension.

The disclosure of the '760 patent

The disclosure of the '760 patent regarding the making of an extract from mycelia of *Lentinus edodes* is at col. 2, line 61 to col. 3, line 20 and is set forth above. This disclosure includes that the enzymes active in digestion of the culture are cellulase, chitinase, glucosidase and protease in the "nutrient medium and the tissue-medium" (col. 3, lines 1-3). Furthermore, the '760 patent describes that the extract acts only upon cancerous cells (col. 2, line 43). The '760 patent discloses administration of the extract prepared as described to rats implanted with an ascites tumor cell line, with inhibition of proliferation of the tumor cells (col. 6). The '760 patent also discloses that the antitumor activity of the extract is related to the enzyme composition of the mycelia (col. 8, line 30-32).

Differences between the claimed invention and the disclosure of the '760 patent

The invention of claim 19 is distinct from what is disclosed in the '760 patent in several respects. First, claim 19 recites a method for treating cancers or tumors by enhancing

LAK activity. This is contrary to the teaching of the '760 patent that the extract disclosed therein acts only upon cancerous cells.

Second, claim 19 recites that the extract that is used is one made by a process that includes adding at least one enzyme that is a cellulase, a protease or a glucosidase to the digestion of the mycelial culture. As has been repeatedly explained above, the '760 patent discloses that the culture should be digested using the enzymes endogenous to the mycelia and expressly relates the obtaining of antitumor activity in the extract to performing the digestion with the enzymes of the mycelia.

The '760 patent does not disclose or suggest the specific modifications of its teachings necessary to make the invention of claim 19. First, there is no suggestion that the extract can be applied in a therapeutic amount to enhance LAK activity in any subject. To the degree the Examiner has relied upon an inherency theory to suggest this element of the claim, Appellants note that the previous rejection for anticipation based upon inherency has been withdrawn.

Second, there is no suggestion that the practitioner should add enzymes to the culture during the digestion. Indeed, there is express teaching in the '760 patent that such should <u>not</u> be done.

Furthermore, the Examiner has not established motivation to one of ordinary skill in the art to make any modification of the teachings of the '760 patent to make the invention of claim 19. As explained above, the Examiner has merely speculated, incorrectly, that the skilled artisan would be motivated to substitute exogenous enzymes for the enzymes endogenous to the culture during the digestion. In fact, the '760 patent expressly states that obtaining antitumor activity in the extract is related to the enzyme composition of the mycelia. Contrary to the allegation of the Examiner, this would motivate the skilled artisan not to add any exogenous enzymes to the culture.

Furthermore, the Examiner has not put on the record any reasons for motivating the skilled artisan to treat a tumor by enhancing LAK activity using the extract. Indeed the '760 patent also provide motivation to the contrary, expressly stating that the extract acts directly upon the tumor cells.

As two elements of *prima facie* obviousness are not established by the Examiner, the rejection of claim 19 under 35 U.S.C. § 103(a) over the '760 patent should be reversed.

IX. Summary

Claims 1-10 and 12-20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '760 patent. The Examiner

has failed to properly establish *prima facie* obviousness of any of the pending claims over the reference, and the rejection should be reversed on this ground alone.

As to claim 20, a process for making an extract, the modification of the teaching of the reference that enzymes should be added to the digestion of the mycelial culture is neither disclosed nor suggested by the '760 patent. Indeed, there is disclosure in the '760 patent that urges against such modification. This disclosure of the '760 patent evidences that the Examiner's proffer of motivation to make that change is mere speculation.

Claims 1-9 are product by process claims that recite the same process steps as claim 20 and the above argument applies to these claims as well.

Claims 12-18 are directed to a method for enhancing LAK activity of lymphocytes. In this instance, the Board should note that the '760 patent only describes use of an extract to directly kill tumor cells. Lymphocytes as a type of cell, whether as killer of tumor cells or as tumor cells *per se*, are not even mentioned in the '760 patent. There is no disclosure whatsoever of the concept of LAK activity and certainly no hint of any extract having activity of enhancing LAK activity of lymphocytes. Thus, the '760 patent fails to describe or suggest

modifications of its teachings necessary to obtain every feature of the invention of claims 12-18.

Furthermore, the Examiner has not made any mention of any motivation, either from the '760 patent or from the state of the prior art, to apply any extract to lymphocytes to enhance their LAK activity.

Claims 3 and 14, dependent upon claims 1 and 12, respectively, include as a feature that a concentration of extract of "1 μg or more per 10^6 lymphocytes" (claim 3 and 14)) is a therapeutically effective amount for enhancing LAK activity of lymphocytes (claim 14). The '760 patent does not disclose or suggest that an extract should be administered at a concentration of any mass per number of lymphocytes. Neither does the '760 patent disclose nor suggest that the concentration should be more than 1 μg per 10^6 lymphocytes.

Furthermore, the Examiner has not stated on the record any source of motivation to modify the teachings of the '760 patent to arrive at the invention of claims 3 and 14.

Finally, claim 19 is directed to a method for treating cancers or tumors by enhancing LAK activity. This claim contains three modifications over the '760 patent that are neither disclosed nor suggested by the reference. In particular, the '760 patent expressly teaches that the extract acts directly on tumor cells. Thus, there is no teaching or

suggestion that a therapeutic amount of extract for enhancing LAK activity should be administered to a subject. Both the therapeutic amount and the enhancement of LAK activity are absent from the disclosure of the '760 patent. Also, the extract used in claim 19 is described as a product of a process, like that of claim 20, in which a culture of mycelia is digested in an aqueous medium containing added enzymes. Again, the '760 patent expressly urges that only the enzymes endogenous to the culture should be used for the digestion.

Furthermore, the Examiner has not put on the record any motivation to one of ordinary skill in the art to make these modifications in the face of the teachings of the '760 patent to the contrary.

Furthermore, there is evidence of record comparing the extract of the invention to the extracts characterized in the '760 patent. Claim 20 is a process of making an extract and claims 1-9 are directed to the extract as a product of the process. The evidence comparing the extract obtained by the process of claim 20 shows that it is substantially different from the LAP, LAP-1 and LAP-2 extracts prepared in the '760 patent. Evidence of differences in the major sugar component between the extract of the invention and the LAP-1 and LAP-2 extracts of the '760 patent has been accepted by the Examiner as

sufficient to overcome a rejection of composition claims based upon inherency.

The Examiner has admitted on the record that the extract of the invention would be expected by one of skill in the art to be identical to that of the '760 patent, because the processes for making the extracts are similar. The Examiner has used this expectation as a basis for a rejection for lack of novelty based upon inherency. Therefore, differences in the products obtained by the process described in the instant claims and the products described in the '760 patent must be considered unexpected by the skilled artisan.

Appellants submit that the evidence of differences in the products of the invention and in the products described in the '760 patent are an unexpected result sufficient to rebut any case of *prima facie* obviousness of claims 1-9 and 20 deemed properly established by the Examiner. The rejection of claims 1-9 and/or 20 under 35 U.S.C. § 103(a) over the '760 patent may be reversed for this reason also.

Claim 10 is a method of using the product of claim 1. If claim 1 is found allowable, claim 10, being a method of use commensurate in scope with an allowable product claim, should also be found allowable.

The standing rejection of at least claims 1-10 also fails as a matter of law. *Prima facie* obviousness is a legal theory

that assigns the burden of proof. Upon establishment by the Examiner of *prima facie* obviousness of the claimed invention, the Applicant (Appellant) must present evidence sufficient to rebut the Examiner's case of obviousness to establish that the claims are patentable.

In the present case, the Examiner has accepted the comparative evidence of record as sufficient to overcome a rejection of claims 1, 2 and 4-11 for lack of novelty based upon a theory of inherency. Thus, the comparative evidence of record has been found sufficient to rebut a presumption of identity, the epitome of obviousness. To then maintain or impose a rejection of claims 1-10 based upon obviousness is legally untenable.

X. Conclusion

The rejection of claims 1-10 and 12-20 under 103(a) over the '760 patent fails and must be reversed as to all of the pending claims because the Examiner has not properly established *prima facie* obviousness of the claimed invention.

As to claims 1-9 and 20, Appellants have also presented evidence of record sufficient to rebut any allegation of *prima facie* obviousness that the Examiner may be deemed to have properly established. This is an additional reason to reverse the rejection as to these claims.

As to claims 1-10, the standing rejection may be found improper as a result of the operation of law. Evidence found sufficient to rebut a presumption of identity based upon inherency over a reference should also be found sufficient to rebut an allegation of *prima facie* obviousness over the same reference.

The favorable action by the Board of reversal of the rejection of claims 1-10 and 12-20 under 103(a) as being unpatentable over the '760 patent, and an order to the Examiner to allow these claims is respectfully requested.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a five (5) month extension of time for filing a response in connection with the present application. An extension of two (2) month(s) for responding to the Final Rejection was previously requested and paid for on October 17, 2003. Thus a fee of $1,590.00 is required to obtain an additional three (3) month(s) for filing the Notice of Appeal.

The required total fee of $1,920.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: APPENDIX

XI. Appendix - Claims on Appeal

1. (previously presented) A LAK activity enhancer containing an extract of Lentinus edodes mycelium, which is prepared by

preparing a suspension by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more additive enzymes selected from the group consisting of cellulase, protease and glucosidase, wherein the solid medium is based on bagasse and defatted rice bran; and

raising the temperature of the suspension to about 80-100°C to inactivate the enzymes.

2. (original) The LAK activity enhancer of claim 1 for enhancing LAK activity by acting on lymphocytes derived from peripheral blood.

3. (original) The LAK activity enhancer of claim 2 containing an extract of Lentinus edodes mycelium at a concentration of 1 μg or more per 10^6 lymphocytes.

4. (original) An LAK activity-enhancing formulation containing the LAK activity enhancer of claim 1.

5. (original) A pharmaceutical or veterinary LAK activity-enhancing formulating comprising the LAK activity enhancer of claim 1 and pharmaceutically acceptable carrier.

6. (original) The LAK activity-enhancing formulation of claim 4 or 5 for oral administration.

7. (original) The LAK activity-enhancing formulation of claim 4 in the form of a food, drink or feed.

8. (original) The LAK activity-enhancing formulation of claim 4 or 5 for injection or percutaneous administration.

9. (previously presented) The LAK activity-enhancing formulation of claim 4, wherein said formulation is used for treating tumor and/or cancer.

10. (previously presented) A method for treating tumor and/or cancer comprising administering an effective amount of the LAK activity-enhancing formulation of claim 4.

12. (previously presented) A method for enhancing LAK activity which comprises administering to a mammal a therapeutically effective amount of LAK activity enhancer

containing an extract of Lentinus edodes mycelium, which is prepared by:

preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase, wherein said solid medium is based on bagasse and defatted rice bran; and

raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).

13. (previously presented) The method of claim 12 wherein said LAK activity enhancer acts on lymphocytes derived from peripheral blood.

14. (previously presented) The method of claim 12 wherein said LAK activity enhancer contains an extract of Lentinus edodes mycelium at a concentration of 1 μg or more per 10^6 lymphocytes.

15. (previously presented) The method of claim 12 wherein said LAK activity enhancer further comprises a pharmaceutically acceptable carrier.

16. (previously presented) The method of claim 12 wherein said LAK activity enhancer is orally administered.

17. (previously presented) The method of claim 12 wherein said LAK activity enhancer is in the form of a food, drink or feed.

18. (previously presented) The method of claim 12 wherein said LAK activity enhancer is administered by injection or a percutaneous route.

19. (previously presented) A method for treating tumor and/or cancer by enhancing LAK activity, which comprises administering a therapeutically effective amount of a LAK activity enhancer containing an extract of Lentinus edodes mycelium that has been extracted from a solid medium comprising bagasse as a base which contains Lentinus edodes mycelia and which is obtainable by the following steps:

delignifying the solid medium;

adding water and one or more enzymes selected from the group consisting of cellulase, protease and glucosidase to the delignified solid medium;

crushing and grinding said delignified solid medium in the presence of said enzyme(s);

inactivating the enzyme(s); and

filtering the resulting suspension.

20. (previously presented) A method of preparing a LAK activity enhancer which comprises

preparing a solution by crushing and delignifying a solid medium containing Lentinus edodes mycelia in the presence of water and one or more of additive enzymes(s) selected from the group consisting of cellulase, protease and glucosidase, wherein said solid medium is based on bagasse and defatted rice bran; and

raising the temperature of said suspension to 80-100°C to inactivate the enzyme(s).